REMARKS

This paper is responsive to the Office Action dated August 25, 2004, which is the second action on the merits of the application.

Claims 13-40 are pending in the application, and stand variously rejected. Certain claims have now been amended, but no claim has been cancelled or added.

Further consideration and allowance of the application is respectfully requested.

Double Patenting

The pending claims stand provisionally rejected for obviousness-type double patenting over certain claims of copending application USSN 10/087,142.

Prosecution of the present application is more advanced than the 10/087,142 application, and applicant expects it to issue as a U.S. Patent first.

The pending claims also stand rejected for obviousness-type double patenting over claims 1-3 of U.S. Patent 6,458,589. The Office Action indicates that the claims in the present application are obvious because the cell populations of the '589 patent have the same characteristics as cells produced by the methods of the instant claims.

Applicant respectfully disagrees. Under an analysis for obviousness-type double patenting, the question is whether the invention defined in a *claim* of the present application is an obvious variation of the invention defined in a *claim* in the cited patent. See. *In re Berg,* 46 USPQ2d 1226 (Fed. Cir 1998), and MPEP § 804 (II)(B)(1)(a) at page 800-23. In other words, it is only the claims of the patent and the application which are to be compared, absent of what is taught in the specification.

The claims in the '589 patent cover a product: namely, a set of cell populations, one of which has certain characteristics of hepatocytes. The claims of the present application cover methods for making such cells *using a histone deacetylase inhibitor.* Nowhere in the claims of the '589 patent does it suggest that the hepatocyte lineage cells can be generated using a histone deacetylase inhibitor.

Withdrawal of this rejection is respectfully requested.

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Rejections under 35 USC § 112

The pending claims stand newly rejected under 35 USC § 112 ¶ 1 as not being enabled for initiating differentiation of the hES cells as an optional step. The Office Action cites an article by Lee et al. (Genesis 38:32, 2004) as teaching that histone deacetylase activity is required for ES cell differentiation.

The undersigned is grateful to the Examiner for bringing the Lee article to his attention, because it helps underline the inventiveness of the methods claimed here. The article implies that histone deacetylase inhibitors would have the effect of inhibiting differentiation of ES cells. Thus, it teaches against the idea of using histone deacetylase inhibitors to make differentiated cell populations.

In contrast, the specification of this application teaches that histone deacetylase inhibitors unexpectedly direct undifferentiated hES cells into a pathway that generates a highly homogeneous population of hepatocyte lineage cells.

One such method involves initiating differentiation *before* culturing with the histone deacetylase inhibitor. In Example 1, differentiation is initiated by forming embryoid bodies. The EB cells are then plated out, and combined with the histone deacetylase inhibitor, producing cells having characteristics of hepatocytes. Alternatively, in Example 9, differentiation is initiated not by making embryoid bodies, but by culturing with DMSO. These examples both confirm that culturing with the histone deacetylase inhibitor can be done *subsequent* to when differentiation is initiated.

The specification also teaches that hepatocyte lineage cells can be made from hES cells with a histone deacetylase inhibitor in contact with the cells *in the initial step.* In Example 5 (page 42), undifferentiated hES cells are maintained in feeder-free culture. Then differentiation towards hepatocyte lineage cells is initiated by replacing the conditioned medium (in which the hES cells were cultured) with medium not containing bFGF, but containing 5 mM sodium butyrate (p. 42, lines 15-16). The undersigned does not know whether the cells start to differentiate because of the presence of the histone deacetylase inhibitor, because of one of the other alterations to the medium, or because of a combination of both. It is unnecessary to know which of these is correct in order to use the invention. The example confirms that differentiation *can* be initiated *simultaneously* to the culturing with the histone deacetylase inhibitor, which again serves to channel the cells along the hepatocyte lineage.

Base claims 13 and 28 have now been amended to indicate explicitly that culturing with the histone deacetylase inhibitor can occur at a time that is *simultaneous or subsequent* to the time at which differentiation is initiated. Both alternatives are enabled in the specification, and illustrated in the working examples.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112 ¶ 2:

Claim 13 stands rejected under 35 USC § 112 ¶ 2 for being unclear as to whether the histone deacetylase inhibitor is used with the cells in which differentiation has been initiated, or with an entirely separate population of hES cells.

The skilled reader would readily recognize that the method is directed to produce a population of hepatocyte lineage cells, and thus the steps are all performed on the same population. Nevertheless, the claims have been amended herein to state explicitly that the cells referred to in step c) are the cells in step b) — which may or may not be predifferentiated before combining with the histone deacetylase inhibitor, as already explained. The same amendment has been made to claim 28.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 102:

Claim 27 stands rejected over a reference by Kaneko et al. The Office Action implies that the claim can be satisfied by obtaining hepatocytes from any source (such as liver tissue), and maintaining them by culturing with butyrate.

The claim has now been amended to require that the user obtain a population of cells having characteristics of hepatocytes from pPS cells. Since the cited reference does not teach how to obtain a population of hepatocyte lineage cells from pPS cells, the claimed method is not anticipated by the reference.

Withdrawal of this rejection is respectfully requested.

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PATENT
10/001,267
Docket 093/004p

Request for Interview

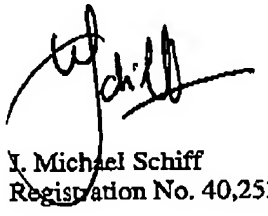
Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

Fees Due

No fee is due for entry or consideration of this Amendment. Nevertheless, should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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